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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,654	ONO ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8,10-14 and 18-25* is/are pending in the application.

4a) Of the above claim(s) *18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-8, and 10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice of Sequence Noncompliance.

DETAILED ACTION

1. Claims 1, 5-8, 10-14 and 18-25 are all the pending claims for this application.

2. Claims 2-4, 9, and 26 were cancelled and Claims 1, 5, 10 and 14 were amended in the Response of 2/26/10.

3. Claims 18-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. The non-elected species of antibody of Claim 14 are withdrawn.

4. Claims 1, 5-8, and 10-14 are the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for rejection. This Office Action is final.

Withdrawal of Objections

Specification

6. The objection to the application because it contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2) is withdrawn.

Applicants have provided sequence identifiers, e.g., at p. 17, in the amendment to the specification in the Response of 2/26/10.

7. The objection to the improper use of trademarks, e.g., "polysorbate 80™", "TaKaRa pyrobest™", in this application is withdrawn.

Applicants have amended the specification in the Response of 2/26/10 to capitalize the trademark(s).

Withdrawal of Rejections

Claim Rejections - 35 USC § 101

8. The rejection of Claims 1-14 and 26 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is moot for cancelled Claim 26 and withdrawn for pending Claims 1, 5-8, and 10-14 in view of Applicants amendment in the Response of 2/26/10 to insert "isolated antibody".

Claim Rejections - 35 USC § 112, second paragraph

9. The rejection of Claims 1-13 and 26 for the recitation "an antibody that "recognizes" a...(TRAIL receptor)" because the genus of TRAIL receptor family of proteins (e.g., DR4, DR5, TRID/DcR1, DcR2, OPG, TRAIL-R3, etc.) is unclear is withdrawn.

Applicants amended Claim 1 in the Response of 2/26/10 to clarify that the TRAIL receptor comprises "a cytoplasmic death domain" which according to the specification on p. 1, lines 20-21, is found in the TRAIL-R1 or TRAIL-R2.

Claim Rejections - 35 USC § 112, first paragraph

Enablement

10. The rejection of Claims 1-13 and under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for antibody fragments having less than the full complement of CDRs or single variable domain antibodies from any TRAIL-R2 antibody is withdrawn.

Claim 1 has been amended to clarify that the antibodies consist of a linker(s) and at least three Fv units. Such antibodies can have H chain-derived three CDRs and four FRs and L chain-derived three CDRs and four FRs for binding to a TRAIL receptor. Thus, "antibody fragments having less than the full complement of CDRs or single variable domain antibodies" are excluded from the amended claims.

Claim Rejections - 35 USC § 102

11. The rejection of Claims 1, 11 and 26 under 35 U.S.C. 102(b) as being anticipated by van Geelen et al. (Br J Cancer. 2003 Jul 21; 89(2):363-73); cited in the PTO 892 form of 5/26/09) is withdrawn.

The claims have been amended to recite that the antibody is at least a trimer or triabody which van Geelen does not teach.

12. The rejection of Claims 1, 11-13 and 26 under 35 U.S.C. 102(b) as being anticipated by Ohtsuka et al. (Oncogene 22:2034-2044 (2003 Apr 3); cited in the PTO 892 form of 5/26/09) is withdrawn.

The claims have been amended to recite that the antibody is at least a trimer or triabody which Ohtsuka does not teach.

13. The rejection of Claims 1, 11-13 and 26 under 35 U.S.C. 102(b) as being anticipated by Ichikawa et al. (Nat. Med. 7:954-960 (2001)) is withdrawn.

The claims have been amended to recite that the antibody is at least a trimer or triabody which Ichikawa does not teach.

14. The rejection of Claims 1-5, 9-13 and 26 under 35 U.S.C. 102(e) as being anticipated by Li et al. (US 20080248037; published 10/9/08; priority to 4/6/04) is withdrawn.

Applicants have perfected their priority (12/12/03) by filing a certified translation of JP 2003-415735 (filed12/12/2003) with the Response of 2/26/10 pursuant to 37 CFR 1.55 and MPEP 201.13.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

15. The rejection of Claims 1, 5-8, and 10-14 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for using any antibody in vivo to induce apoptosis in any human cancer subject is maintained.

The rejection was set forth in the Office Action of 9/1/09 as follows:

Nature of the Invention/ Skill in the Art

> "Claims 1 and 11 are interpreted as being drawn to an antibody that binds TRAIL-R2 (DR5). Claims 12 and 13 depend from Claim 1 and are drawn to the antibody having the ability to induce apoptosis (Claim 12) in any cancer cell (Claim 13). Claim 26 is drawn to the pharmaceutical composition comprising the antibody of Claim 1. All the remaining and dependent claims fall under the rejection. The claims are examined for an implied intended use of inducing apoptosis in any cancer cell in vitro much less vivo including occurring within a human subject.

The relative skill in the art is a Ph.D. or M.D. with a background in immunotherapeutics.

Disclosure in the Specification

The working examples of cytotoxic, apoptosis-inducing TRAIL-R2 antibodies are described in Section 4 (pp. 40-41) of the specification:

The data for cytotoxic activity of TRAIL-R2 diabodies on COLO 205 cancer cells in vitro are shown in Fig. 1. The cell count did not decrease after addition of the diabody alone, suggesting that the diabody has no cytotoxic activity by itself, and cytotoxic activity was detected when M2 antibody was added to crosslink the diabody. This suggests that apoptotic signals are transmitted when the polymerization of TRAIL receptor on the surface of cell membranes is enhanced.

The data for cytotoxic activity of TRAIL-R2 triabodies on COLO 205 cancer cells in vitro are shown in Fig. 2. The results showed that neither the diabodies nor whole IgG had marked cytotoxic activity. In contrast, the cell count was dramatically decreased after addition of the triabody, suggesting that the triabody had obvious cytotoxic activity with the activity significantly higher when the triabody had the 1-mer or O-mer linker.

The data for cytotoxic activity compared between the triabody and tandem diabody on COLO 205 cancer cells in vitro are shown in Fig. 3. This result showed that the activity of the tandem diabody was stronger than that of the triabody, and was equivalent to or greater than that of the natural ligand Apo2L. These results suggest that of the molecules tested, the tandem diabody by itself is the most effective molecule.

Applicants have demonstrated that different multivalent forms of a TRAIL-R2 antibody can produce vastly different cytotoxicity profiles within the same cancer cell in vitro. Applicants contemplate using this as a method of treatment for tumors in being formulated into pharmaceutical compositions. None of the working examples demonstrate a relevant animal disease model correlate considering the TRAIL-R2 antibody effects on mediating apoptosis on a tumor target cell in vivo. The specification does not disclose whether the method is effective in animals with a pre-existing TRAIL-R2-expressing tumor, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing intended in vivo effects, especially inducing apoptosis in a pre-existing neoplasia is a significant omission especially in view of the status of the field. Therefore, it appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification alone and the specification fails to enable the use of anti-TRAIL-R2 antibodies for tumor therapy in vivo via induction of apoptosis.

Prior Art Status: TRAIL-R2 antibodies have some in vivo applicability for inducing apoptosis in cancers

Yagita et al. (Cancer 95:777-783 (10/2004)) provides an overview of immunotherapeutics for TRAIL-R2 (DR5) at the time of application filing and beginning on p. 779, Col. 1, describes anti-human DR5 antibodies having been shown to induce apoptosis in melanoma cell lines in vitro, and the TRA-8 (DR5) antibody of Ichikawa (discussed below) inducing tumoricidal activity in mouse xenografts. Yagita discuss the status of immunotherapeutics stating:

> "The potential toxicity in pathological conditions may also be a concern as discussed with rTRAIL. A recent study has shown that the anti-tumor effects of anti-human DR5 Mabs were synergistically enhanced in vitro by combination with chemotherapeutic drugs such as adriamycin and cisplatin. However, the potential toxicity in the combination therapy is again a concern, as discussed for rTRAIL. Although the potential toxicity remains to be determined, Human Genome Sciences and Cambridge Antibody Technology are now planning to initiate a phase I clinical trial of an agonistic humanized anti-DR5 mAb (HGS-ETR2) in patients with advanced tumors in the UK" (p. 780, Col. 1, ¶1).

> "Therefore, anti-DR5 mAb may be more beneficial than rTRAIL for cancer therapy, because it not only primarily eliminates most TRAIL-sensitive tumor cells at the time of administration, but also secondarily induces tumor specific effector and memory T cells that can eradicate even TRAIL-resistant tumor variants and provide long-term protection from tumor recurrence" (p. 780, Col. 1, ¶2).

Wakalee et al. (Ann. Oncol. On-line publication 7/24/09) reports on the phase I results for the HGS-ETR2 antibody mentioned in Yagita showing that the antibody represent a novel approach to treating solid tumors disclosed in Table 1 (***NSCLC, soft tissue sarcoma, prostate, renal, NHL and breast***). Of twenty-seven patients, stable disease was seen in 9 patients with a variety of tumor types. The phase I study of the antibody every 21 days documented disease stability in 12 of 37 patients and the study establishes a single agnet does of HGS-ETR2 where the future development should focus on better identification of patients and on combination regimens. Further, detection of TRAIL-R2 by immunohistichemistry has not correlated with response to the agent in preclinical models, so effects to detect other markers that may more accurately predict response should be considered.

Ichikawa et al. (Nat. Med. 7:954-960 (2001)) teach that the anti-TRAIL-R2 Mab, TRA-8, was tumoricidal for ***human astrocytoma cell line, 1321N1, and human leukemic Jurkat cell line*** in SCID mice (Fig. 4), suggesting that TRA-8 is a potent inhibitor of in vivo tumor-cell growth, and that the inhibition is mediated by apoptosis.

Miller et al. (WO 01/77342; published 10/18/01; cited in the IDS of 9/30/08) discloses in Figures 12A-E apoptosis induced by an anti-DR5 tetravalent antibody (16E2 Octopus), an anti-DR5 bivalent IgG antibody (16E2 IgG), and Apo2L/TRAIL (Apo2L) on cancer cell lines: COLO 205 (Fig. 12A), SK-MES-1 (Fig. 12B), HCT116 (Fig. 12C), and HOP 92 (Fig. 12D), compared to a non-cancer control cell line, HUMEC (Fig. 12E); Figure 14 represents the *in vivo* activity of Apo2L/TRAIL (60mg/kg, 5x/week), 3H3 bivalent IgG (5mg/kg given days 0, 3, 5 and 9), 16E2 bivalent IgG (16E2) (5mg/kg given days 0, 3, 5 and 9), and 16E2 Octopus (5mg/kg given days 0, 3, 5 and 9) with respect to ***COLO 205*** tumors in athymic nude mice; and Figure. 15 represents an alamarBlue in vitro assay confirming the apoptotic activity of the material used in the mouse studies (Apo2L/TRAIL and 16E2 Octopus) as compared to an Apo2L standard positive control.

Under MPEP 2164.02 ("Working Example"): The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

Thus for at least human colon cancer cells, *COLO 205*, Applicants own working examples and the working examples in the prior art demonstrate that antibody-targeting of TRAIL-R2 in human colon cancer is achievable and can mediate an apoptotic endpoint in the cancer cell whether in vitro or in vivo. Additionally, the HGS-ETR2 antibody and the TRA-8 antibody each appear to be successful in some in vivo cancer therapy animal models.

Unpredictability/ Undue Experimentation

Therefore, due the unpredictability of immunotherapeutics in general, and in view of the insufficient guidance and/or working examples concerning the use the claimed antibodies as immunotherapeutic agents, one skilled in the art would not know how to practice the broadly claimed invention, i.e., administer anti-TRAIL-R2 antibodies for the apoptosis inducing effect in any cancer cell and its accompanying pathologies without undue experimentation.

Applicants allegations on pp. 9 of the Response of 2/26/10 have been considered and are not found persuasive. Applicants allege whether in vivo data are shown for human subjects is irrelevant when determining the enablement of the claimed antibodies. The Examples of the present application demonstrate that the presently claimed antibodies, which comprise at least three Fv units, can be produced and promote apoptosis. That is, the present disclosure provides enablement for the antibodies recited in the pending claims.

Response to Arguments

MPEP 806.04(d) states in part "In general, a generic claim should require no material element additional to those required by the species claims, and each of the

species claims must require all the limitations of the generic claim." In other words, a generic claim embraces all species claims, thus Applicants allegations that "whether in vivo data are shown for human subjects is irrelevant when determining the enablement of the claimed antibodies" would appear to be contrary to the rules. Dependent Claims 12 and 13 require that the antibody induces apoptosis in a cell where the cell is a tumor cell. The claims encompass any kind of tumor cell occurring in vitro or in vivo in any mammal including a human. The rejection is maintained.

Priority

16. Applicants have filed a certified translation of the foreign priority paper, i.e., JP 2003-415735 (filed12/12/2003) with the Response of 2/26/10 to overcome the art rejection(s). Accordingly, for purposes of applying art, the instant claims are now given the priority filing date of *12/12/03*.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. The rejection of Claims 1, 5-8, and 10-13 under 35 U.S.C. 102(b) as being anticipated by Miller et al. (WO 01/77342; published 10/18/01; cited in the IDS of 9/30/08) is maintained.

For review, the rejection was set forth in the Office Action of 9/1/09 as follows:

. "The interpretation of Claims 1-5, 9-13 and 26 is discussed above under sections 16-18. Claims 6-8 are interpreted as being drawn to the linker for the scfv of Claim 5 having 0 to 2 amino acids (Claim 6), or 0 amino acids (Claim 7) or 1 amino acid (Claim 8).

Miller discloses in Figures 12A-E apoptosis induced by an anti-DR5 tetravalent antibody (16E2 Octopus), an anti-DR5 bivalent IgG antibody (16E2 IgG), and Apo2L/TRAIL (Apo2L) on cancer cell lines: COLO 205 (Fig. 12A), SK-MES-1 (Fig. 12B), HCT116 (Fig. 12C), and HOP 92 (Fig. 12D), compared to a non-cancer control cell line, HUMEC (Fig. 12E); Figure 14 represents the in vivo activity of Apo2L/TRAIL (60mg/kg, 5x/week), 3H3 bivalent IgG (5mg/kg given days 0, 3, 5 and 9), 16E2 bivalent IgG (16E2) (5mg/kg given days 0, 3, 5 and 9), and 16E2 Octopus (5mg/kg given days 0, 3, 5 and 9) with respect to COLO 205 tumors in athymic nude mice; and Figure. 15 represents an alamarBlue in vitro assay confirming the apoptotic activity of the material used in the mouse studies (Apo2L/TRAIL and 16E2 Octopus) as compared to an Apo2L standard positive control. Miller discloses polypeptide chains such as scfv comprising the VH and VL domains linked by an amino acid X1 or X2 of 0 to 1 residues (p. 14, lines 1-4); or 2 to about 10 amino acid residues, and most preferably four or less residues (p. 30, lines 32-33)."

Applicants allege on p. 10 of the Response of 2/26/10 "the antibodies of Miller et al. contain Fc regions or constant region fragments. Miller et al. do not disclose "an antibody consisting of a linker(s) and at lease three Fv units". Thus, the amended claims are novel over Miller et al."

Response to Arguments

Miller teaches on p. 42, lines 8-13:

"The multivalent antibody may also comprise a polypeptide chain comprising the formula: (a) VL-CL-flexible linker-VL-CL-flexible linker-VL-CL; In this embodiment, the polypeptide may comprise three to about eight VL-CL polypeptides joined by flexlible linkers....(c) (VL-CL), wherein n is three or more more (e.g. three to about eight, but preferably three or four);...."

Applicants specification defines an Fv unit as a VH-VL where on p. 12 it states:

""Fv" is a dimer (VH-VL dimer) consisting of one unit of VH and one unit of VL bound very strongly by non-covalent bonding. The three complementarity determining regions (CDRs) of each variable region interact with each other, thereby forming an

antigen binding site on the surface of the VH-VL dimer. Six CDRs confer an antigen binding site to the antibody."

The rejection is maintained.

New Grounds for Objection

Sequence Listing

18. The Sequence Listing filed 2/26/10 has been objected to by STIC for the reasons set forth on the attached Raw Sequence Listing report and the Notice of Sequence Non-Compliance. The period of time of responding to this objection is set to expire 3 months from the date of this communication. Extensions of time are available under the provisions of 37 CFR 1.136(a).

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 10 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 10 is rejected because it is drawn to a limitation outside of the scope for the antibody recited in Claim 1. The antibody of claim 1 and dependent claims thereof is required to be at least a trimer or triabody, but dependent Claim 10 requires two scFv molecules which is technically a dimer or diabody.

b) Claim 14 is rejected because it is drawn to a limitation outside of the scope for the antibody recited in Claim 1. The antibody of claim 1 and dependent claims thereof is required to be at least a trimer or triabody, but dependent Claim 14 requires a dimer (a tandem diabody) of an antibody with the amino acid sequence shown in SEQ ID NO: 8.

Conclusion

20. No claims are allowed

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner
Art Unit 1643